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EXAMINER	
BERTAGNA, ANGELA MARIE	
ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/501,834	HARRIS ET AL.	
	Examiner	Art Unit	
	Angela M. Bertagna	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *103* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *103* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. Applicant's response filed on September 29, 2009 is acknowledged. Claim 103 is currently pending. In the response, Applicant canceled claims 1, 2, 5, 8-13, 16-19, 29-37, 40, 43-60, and 104-108.

Applicant's arguments filed on September 29, 2009 have been fully considered, but they were not persuasive for the reasons set forth in the "Response to Arguments" section. Accordingly, this Office Action is made **FINAL**.

Claim Rejections - 35 USC § 112, 1st paragraph (Enablement)

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 103 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the

prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The nature of the invention

Claim 103 is drawn to a method for diagnosing autosomal recessive polycystic kidney disease (ARPKD) in a subject by detecting one or more disease-associated sequence variants of the *PKHD1* gene in a nucleic acid sample obtained from the subject. The invention is classified in the unpredictable arts of chemistry and biology.

The breadth of the claims

Claim 103 is broadly to diagnosing autosomal recessive polycystic kidney disease (ARPKD) in a subject solely by detecting one or more disease-associated sequence variants of the *PKHD1* gene in a nucleic acid sample obtained from the subject. Claim 103 encompasses diagnosis of ARPKD of any degree of severity in any subject (*e.g.* any mammal or a human from any ethnic population) based solely on the detection of at least one disease-associated sequence variant of the *PKHD1* gene. The claim also encompasses diagnosis of ARPKD based on the detection of any sequence variant in the *PKHD1* gene that may later be determined to be associated with ARPKD.

State of the Art and Unpredictability

The prior art of Zerres et al. (Nature Genetics (1994) 7: 429-432; cited previously) and Park et al. (Genomics (1999) 57: 249-255; cited previously) teach that a region of chromosome 6 contains a gene that is associated with ARPKD (see abstract and pages 430-431 of Zerres and

the abstract and pages 254-255 of Park). The prior art does not identify the *PKHD1* gene or any sequence variants thereof as being associated with ARPKD. The post-filing art of Onuchic et al. (American Journal of Human Genetics (2002) 70(5): 1305-1317; cited previously) and Ward et al. (Nature Genetics (2002) 30: 259-269; cited previously) describes the cloning of the human *PKHD1* gene and several mutations within the gene that may be associated with ARPKD (see abstract and pages 1306 and 1309-1312 of Onuchic and the abstract and pages 261-263 and 265 of Ward). Later studies by Rossetti et al. (Kidney International (2003) 64: 391-403; cited previously), Sharp et al. (Journal of Medical Genetics (2005) 42: 336-349; cited previously), and Bergmann et al. (Journal of Human Genetics (2006) 51: 788-793; cited previously) identified additional mutations in the *PKHD1* gene that may be associated with ARPKD (see the abstract and pages 393-400 of Rossetti, the abstract and pages 337-346 of Sharp, and the abstract and pages 790-792 of Bergmann).

The teachings of Rossetti, Sharp, and Bergmann emphasize that diagnosis of ARPKD based on the detection of sequence variants in the *PKHD1* gene is highly unpredictable. For example, Rossetti states, "Although many mutations have now been identified in *PKHD1* the prospects for gene-based diagnostics still appear difficult. In particular, the relative low level of mutation detection in moderate ARPKD patients and clearly defining a *PKHD1* mutation are problematic. Undoubtedly, the identification of more common mutations, especially in particular populations, will aid molecular diagnostics in those locations. As further mutations are defined, and the identity of disease associated changes and polymorphisms can be more clearly established, the prospects for gene-based diagnostics will improve" (page 403). Likewise, Bergmann states, "Overall, the large size of *PKHD1*, its complex pattern of splicing,

multiple allelism and lack of knowledge of the encoded protein's/proteins' functions pose significant challenges to DNA-based diagnostic testing. Nucleotide substitutions, particularly if residing in regulatory elements or introns outside the splice consensus sites, are often difficult to assess without further functional analyses and cannot be unambiguously classified as disease-associated. Investigations on the transcript level, however, are hampered as *PKHD1* is not widely expressed in blood lymphocytes" (abstract). Sharp further supports the conclusion that there is a high degree of unpredictability associated with the use of *PKHD1* mutations for ARPKD diagnosis by stating, "However, the mechanisms by which *PKHD1* mutations cause clinical disease phenotypes are not well understood. Gene based analyses have been complicated by the large gene size and reported mutation detection rates have ranged from 47% to 61%. The limited mutation detection rates and the absence of mutational hot spots in *PKHD1* have confounded efforts to examine potential genotype-phenotype correlations. These methodological challenges must be overcome before such correlative analyses are revealing and gene based examination is robust enough for clinical diagnostic testing" (page 336). Sharp further teaches that the assessment of missense mutations remains problematic, and there is disagreement in the art regarding the proper criteria for determining that a particular mutation is pathogenic (page 347).

The art is also replete with evidence that gene association studies are typically wrong. For example, Lucentini et al (The Scientist (2004) Vol 18; cited previously) titled his article "Gene Association Studies Typically Wrong" and stated, "Two recent studies found that typically, when a finding is first published linking a given gene with a complex disease, there is only roughly a one-third chance that studies will reliably confirm the finding (see page 2 of the

reference). This is consistent with the teaching of Wacholder et al (Journal of the National Cancer Institute (2004) 96(6): 434-442; cited previously) who states, "Too many reports of associations between genetic variants and common cancer sites and other complex diseases are false positives" (abstract). Ioannidis et al. (Nature genetics (2001) 29:306-309; cited previously) further supports this conclusion in pointing out the heterogeneity of results among different studies of genetic polymorphisms (see the abstract, for example).

Guidance in the Specification and Working Examples

The specification discloses the complete nucleic acid sequence of the human *PKHD1* gene as well as the rat and mouse homologs (see Figures 1-13, pages 9-11, and pages 41-48). The specification also teaches a large number of sequence variants in the human *PKHD1* gene and states that sequence variants in the *PKHD1* gene can be used to diagnose ARPKD (see page 2, lines 2-8, page 6, line 27 - page 8, line 16, and pages 31-34).

Working examples 1, 4, and 8 are relevant to the claimed method. In Examples 1, 4, 8, and 9, genomic DNA obtained from ARPKD patients and their family members was analyzed for the presence of mutations in the *PKHD1* gene by Southern blotting, denaturing high performance liquid chromatography, and direct sequencing (see pages 37-40, 48, 54-56, 61-74). The working examples teach that segregation of the observed variants was tested in families where possible (pages 49, 62, and 66). The examples also teach that missense mutations or sequence variants predicted to truncate the *PKHD1* protein were classified as "likely pathogenic changes" (page 49). Normal chromosomes were also analyzed to determine whether the observed missense mutations exist in the normal population (pages 49, 62, and 66). The

missense mutations observed in the human *PKHD1* gene were also analyzed with respect to the mouse ortholog to determine the level of sequence conservation present in and near the mutation site (page 49).

However, the working examples do not teach using the observed sequence variants to diagnose ARPKD in any subject of unknown disease status. The specification also does not include functional analysis of the observed sequence variants at the protein or mRNA level.

Quantity of Experimentation

The quantity of experimentation in this area is immense, since there is complete variability as to whether or not a particular sequence variant is capable of functioning as a reliable diagnostic agent. It would require significant study and experimentation including trials with hundreds of patients from multiple ethnic populations to determine that a single sequence variant in the *PKHD1* gene is capable of reliably functioning to diagnose ARPKD. This would be an inventive, unpredictable and difficult undertaking in itself, and the efficacy of the sequence variant as a diagnostic indicator for ARPKD would need to be demonstrated in a variety of patients with a statistically significant result. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Wacholder notes that in studies of the association of mutations with specific diseases larger studies with 1500 participants have significantly more statistical power than smaller studies (page 435). The post-filing art of Sharp, Bergmann, and Rossetti also supports the conclusion that the claimed method requires an extensive amount of non-routine and

unpredictable experimentation. Each of these research groups conducted extensive validation and functional analysis of observed sequence variants in the *PKHD1* gene, and despite this extensive amount of non-routine experimentation, none of the groups considered any of the studied sequence variants to be sufficient alone to diagnose ARPKD in patients with unknown disease status.

Thus, the teachings in the art support the conclusion that a large quantity of experimentation, with the use of many hundreds, perhaps even thousands, of patient samples would be necessary to demonstrate the ability of even one of the large number of sequence variants encompassed by the claimed method can function to diagnose ARPKD in a single subject population. Each different sequence variant and each different subject population encompassed by the claim would require this large amount of unpredictable and non-routine experimentation.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the level of unpredictability in the ability of any sequence variant in the *PKHD1* gene to diagnose ARPKD in any subject, where the specification only describes the presence of mutations and not their diagnostic capability, combined with the negative teachings in the art of Rossetti, Bergmann, and Sharp regarding the use of *PKDH1* mutation analysis for ARPKD diagnosis and the negative teachings of

Wacholder, Ioannidis, and Lucentini regarding association studies in general, supports a finding of undue experimentation. Given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required, the limited guidance provided in the specification, the limitations of the working examples, and the negative teachings in the prior art balanced only against the high skill level in the art, the inevitable conclusion is that it would require undue experimentation for one of skill in the art to practice the claimed method.

Claim Rejections - 35 USC § 112, 1st paragraph (Written Description)

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 103 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The central inquiry when considering written description is whether an ordinary artisan would reasonably conclude that Applicant was in possession of the claimed invention at the time of filing (see MPEP 2163 and *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1566-67, 43 USPQ2d 1398, 1404-05 (Fed. Cir. 1997); *Hyatt v. Boone*, 146 F.3d 1348, 1354, 47 USPQ2d 1128, 1132 (Fed. Cir. 1998)).

According to Revision I of the Written Description Training Materials (posted 4/11/08 at http://www.uspto.gov/web/menu/written/pdf), the following factors should be considered, when evaluating a claim for compliance with the written description requirement: (a) actual reduction to practice, (b) disclosure of drawings or structural chemical formulas (c) sufficient relevant identifying characteristics (d) method of making the claimed invention, (e) level of skill and knowledge in the art, and (f) predictability in the art (see page 1 of the Training Materials).

Claim 103 is drawn to a method for diagnosing autosomal recessive polycystic kidney disease (ARPKD) in a subject by detecting the presence of one or more disease-associated sequence variants of the *PKHD1* gene. Claim 103 is very broad in scope, encompassing the diagnosis of ARPKD of any degree of severity in any subject (*e.g.* any mammal or a human from any ethnic population) based solely on the detection of at least one disease-associated sequence variant of the *PKHD1* gene. Claim 103 also encompasses diagnosis of ARPKD based on the detection of any sequence variant in the *PKHD1* gene that may later be determined to be associated with ARPKD.

The specification discloses the complete nucleic acid sequence of the human *PKHD1* gene as well as the rat and mouse homologs (see Figures 1-13, pages 9-11, and pages 41-48). The specification also teaches a large number of sequence variants in the human *PKHD1* gene and states that sequence variants in the *PKHD1* gene can be used to diagnose ARPKD (see page 2, lines 2-8, page 6, line 27 - page 8, line 16, and pages 31-34). In Examples 1, 4, 8, and 9, genomic DNA obtained from ARPKD patients and their family members was analyzed for the presence of mutations in the *PKHD1* gene by Southern blotting, denaturing high performance

liquid chromatography, and direct sequencing (see pages 37-40, 48, 54-56, 61-74). The working examples teach that segregation of the observed variants was tested in families where possible (pages 49, 62, and 66). The examples also teach that missense mutations or sequence variants predicted to truncate the *PKHD1* protein were classified as "likely pathogenic changes" (page 49). Normal chromosomes were also analyzed to determine whether the observed missense mutations exist in the normal population (pages 49, 62, and 66). The missense mutations observed in the human *PKHD1* gene were also analyzed with respect to the mouse ortholog to determine the level of sequence conservation present in and near the mutation site (page 49).

However, the working examples do not teach using the observed sequence variants to diagnose ARPKD in any subject of unknown disease status. The specification also does not include functional analysis of the observed sequence variants at the protein or mRNA level. As a result, the specification does not contain an actual reduction to practice of the claimed method. The specification also fails to teach the relevant identifying characteristics required to satisfy the written description requirement. Although methods of evaluating the observed mutations for their diagnostic capabilities are discussed in the working examples, the specification does not contain an example of even a single sequence variant that can be used to reliably diagnose ARPKD in patients of unknown disease status. Since, as evidenced by the teachings of Sharp (see page 347), there is considerable debate in the art regarding the proper criteria for evaluating the diagnostic capability of sequence variants, the ordinary artisan would not be able to readily identify a particular mutation in the *PKHD1* gene as diagnostic for ARPKD or associated with ARPKD, particularly since no diagnostic sequence variants of the

PKHD1 gene were known in the art at the time of filing. As discussed above, the claimed method is associated with a high level of unpredictability, and as a result, the level of skill in the art required to practice the claimed method is high. Therefore, it must be concluded that Applicant was not in possession of the full scope of the claimed method at the time of filing.

Response to Arguments

4. Applicant's arguments filed on September 29, 2009, regarding the rejection of claim 103 under 35 U.S.C. 112, first paragraph for failing to comply with the enablement and written description requirements, have been fully considered, but they were not persuasive.

Regarding the enablement rejection, Applicant first states that the proper standard for assessing compliance with the enablement rejection is whether the ordinary artisan could make and/or use the claimed invention without undue experimentation (page 3). Applicant also states that a considerable amount of routine and predictable experimentation is permissible, and that, since the specification is presumed to be enabling, the burden lies with the PTO to demonstrate otherwise (page 3).

Applicant then argues that the evidence presented in the rejection fails to demonstrate that an undue amount of unpredictable experimentation would be required to enable the claimed method in view of the guidance presented in the specification, and, in particular, in the working examples (pages 3-4). Applicant argues that Example 4 and Tables 6-8 describe diagnostically useful (*i.e.* ARPKD-associated) sequence variants present in the human *PKHD1* gene, and that, in view of this disclosure in the specification, only routine and predictable experimentation

would be required to practice the claimed method for diagnosing ARPKD in a subject based on the detection of one or more ARPKD-associated sequence variants (pages 3-4).

This argument was not persuasive, because the teachings in the cited references establish that the identification of mutations present in the *PKHD1* gene of individuals known to have ARPKD, for example, via the methods described in the working examples of the instant application, does not necessarily indicate that the mutations are diagnostically useful. Rather, as evidenced by the teachings of the cited Bergmann, Sharp, and Rossetti references, the identification of mutations in the *PKHD1* gene of individuals known to have ARPKD constitutes an invitation to conduct further investigation to determine that the mutations are, in fact, diagnostically useful. Also, as discussed above, the cited references establish that a large amount of unpredictable and non-routine experimentation would be required to assess the ability of each identified sequence variant to be useful in the diagnosis of ARPKD. Accordingly, in view of the teachings of Sharp, Bergmann, and Rossetti, the disclosure of the specification, particularly in the working examples, cannot be considered to constitute an enabling disclosure, because the ordinary artisan would have to conduct a significant amount of unpredictable and non-routine additional experimentation to enable the claimed method.

Applicant also argues that the cited references do not indicate that the claimed method is unpredictable (pages 4-5). In particular, Applicant argues that, although Bergmann teaches that predicting the functional consequences and clinical manifestations of *PKHD1* sequence variants is difficult, this is unrelated to a diagnostic method, such as the claimed method, that is not based on functional analysis (page 4). Moreover, Applicant argues, Bergmann teaches at pages 789 and 792 that the disclosed *PKHD1* sequence variants can be used to diagnose ARPKD

(page 4). Applicant also argues that, like Bergmann, the Rossetti and Sharp references teach that the disclosed *PKHD1* sequence variants can be used to diagnose ARPKD (pages 4-5).

This argument was not persuasive, because successful practice of the claimed method necessarily requires functional analysis of each of the *PKHD1* sequence variants in order to determine whether or not they are associated with ARPKD. As discussed in Rossetti, Bergmann, and Sharp, functional analysis is critical for identifying sequence variants observed in the *PKHD1* gene as pathogenic (*i.e.* ARPKD-associated) or merely polymorphic (*i.e.* not useful for diagnosing ARPKD). Since neither the specification nor the prior art had identified any pathogenic *PKHD1* mutations, the unpredictable functional analysis described by Sharp, Rossetti, and Bergmann would be required in order to practice the method of claim 103. Furthermore, in contrast to Applicant's arguments, Bergmann does not teach diagnosis of a subject of unknown ARPKD status based on the detection of a sequence variant at pages 789 and 792. Rather, these sections of the Bergmann describe which mutations in the *PKHD1* gene identified by the prior art are likely to be disease-associated and demonstrate that one mutation, specifically a particular mutation that results in a splicing change, is likely to be ARPKD-associated, and therefore, diagnostically useful. Applicant's arguments regarding the teachings of Sharp were also unpersuasive, because Sharp does not demonstrate that subjects of unknown ARPKD status can be successfully diagnosed based on the detection of mutations in the *PKHD1* gene. Rather, Sharp, like Bergmann and Rossetti, assessed the likelihood that novel and/or previously discovered mutations in the *PKHD1* gene would be suitable for use in methods of diagnosing ARPKD.

Applicant's arguments summarized above regarding Rossetti were also unpersuasive. In contrast to Applicant's arguments, Rossetti does not demonstrate that subjects of unknown ARPKD status can be successfully diagnosed based on the detection of *PKHD1* mutations. Rossetti also teaches that the possibility of diagnosing moderate forms of ARPKD based on the detection of one or more mutations in the *PKHD1* gene is especially problematic (page 401). Furthermore, Rossetti provides an extensive discussion of the difficulties inherent in diagnosing ARPKD based on the detection of disease-associated mutations, stating (see pages 401-402, where emphasis has been added by the examiner):

> **A problem that has been highlighted here is defining what is a mutation in this disorder.** The group of truncating and typical splicing mutations are clearly disease associated. Missense changes that are frequently found in ARPKD, segregate appropriately, change highly conserved residues, and were not detected in the normal population (such as T36M, I222V, and C3346R) can also be fairly safely considered mutations. **However, it is much less straightforward to categorize some of the remaining missense changes and potential splice changes situated distant from the canonic sequences. This was evident in this study where in five patients three potential mutations were identified and, using the mutation criteria we defined of testing segregation and absence in the normal population, we were unable to exclude one as a polymorphism. One potential mutation, T2869K, illustrates the dilemma. It was present in several of these pedigrees and, although this residue is not strongly conserved (being valine in the mouse), it is a relatively nonconservative change. Furthermore, it was not found in our screen of normal chromosomes and present in several ARPKD pedigrees.** Another example of the uncertainty is the change (D/Y3139) that we have defined as a polymorphism (because of its presence in the normal population) but was previously defined as a mutation. Of course, presence in the normal population is not sufficient to exclude a change as a disease-associated mutation in a recessive disorder, although given the estimated carrier frequency (1 of 70) and the large number

> of different mutations, the prevalence of any individual mutation would be expected to be low in the normal population. As data become available from more studies, enrichment of a change in the ARPKD population and segregation consistent with pathogenicity may be the best evidence that it is disease associated. **However, whether a change is a mutation or a polymorphism may be something of a gray area in ARPKD, dependent on what combination of alleles are found in an individual or even the combination of changes on an allele. For instance, if one allele is a hypomorphic missense mutation, coinheritance of an inactivating change may be sufficient to cause disease. Whereas, in combination with another hypomorphic allele, that same mutation may not cause disease, or the disease may be milder.** A similar situation with the R229Q mutation/polymorphism in *NPHS2* has recently been described in late-onset focal segmental glomerulosclerosis. **The description of further mutations and phenotype/genotype studies will be required to resolve this uncertainty** (see below).

Thus, the teachings of Rossetti cited above in combination with the teachings of the reference in the last paragraph on page 403 (cited above in the rejection) and those of Sharp and Bergmann cited in the rejection clearly indicate that the identification of ARPKD-associated mutations in the *PKHD1* gene is a difficult endeavor that is associated with a high degree of unpredictability.

Finally, it is important to note that the Bergmann, Rossetti, and Sharp references were all published after the filing date of the instant application. Thus, even years after the filing date of the instant application, practitioners in the art considered methods, such as the claimed method, of diagnosing ARPKD based on the detection of a disease-associated mutation in the *PKHD1* gene to be associated with a high degree of unpredictability and also to require a large amount of non-routine experimentation to identify mutations in the *PKHD1* gene as pathogenic,

and therefore, diagnostically useful. This highlights the inherent unpredictability and large quantity of experimentation associated with the claimed method.

Applicant also argues that the claimed method, which functions to detect sequence variants of the *PKHD1* gene that are diagnostic for ARPKD, is distinct from large-scale genetic association studies, which are designed to correlate the presence of sequence variants with the development of complex diseases, and as a result, do not require the large amount of validation necessary for large-scale genetic association studies (page 5). Applicant also argues that functional analysis is irrelevant to the claimed method and not required for its successful practice (page 5).

Applicant's first argument was not persuasive, because, although the claimed method is not identical to the large-scale genomic association studies described in Wacholder, Ioannidis, and Lucentini, the teachings of these references are reasonably pertinent to the claimed method, in which disease-associated mutations in the *PKHD1* gene are used to diagnose ARPKD. As discussed above, the teachings of Wacholder, Ioannidis, and Lucentini establish that the correlation of a particular mutation with a disease is necessarily unpredictable and requires extensive validation and consideration of the functional consequences of the mutation. Accordingly, the ordinary artisan would have recognized from the cited teachings of Wacholder, Ioannidis, and Lucentini that any method based on the association of a particular mutation with a disease, such as the claimed method of using ARPKD-associated mutations to diagnose ARPKD, is necessarily associated with a high degree of unpredictability and requires a large quantity of non-routine validation experimentation using some amount of population analysis and also structure-function analysis. This analysis of the teachings of Wacholder,

Ioannidis, and Lucentini is consistent with the teachings of Rossetti, Sharp, and Bergmann, which as discussed above, indicate that identifying ARPKD-associated mutations in the *PKHD1* gene is unpredictable and requires a large amount of non-routine experimentation. Applicant's second argument was also unpersuasive, because functional analysis is a critical factor in the determination of whether a particular sequence variant identified in the *PKHD1* gene is a disease-associated mutation or simply a polymorphism. This is supported by the teachings of Rossetti, for example, at pages 402-403, where the reference emphasizes that structure-function analysis is critical in determining whether a particular sequence variant identified in the *PKHD1* gene is actually a disease-associated mutation or simply a polymorphism.

Since Applicant's arguments were not persuasive, the rejection of claim 103 under 35 U.S.C. 112, first paragraph (enablement) has been maintained.

Regarding the written description rejection, Applicant argues that, in view of the disclosure of the specification, and especially the disclosure present in the working examples, and the deficiencies in the art cited in the rejection, the ordinary artisan would recognize that the Applicant was in possession of the claimed invention (page 6).

This argument was not persuasive, because although the specification demonstrates that the Applicant was in possession of a method for screening nucleic acid samples obtained from subjects of known ARPKD status for mutations in the *PKHD1* gene present in ARPKD subjects (see, for example, working examples 4, 8, and 9), the specification does not demonstrate that the Applicant was in possession of a method for diagnosing ARPKD in a subject of unknown disease status based on the detection of one or more disease-associated mutations in the *PKHD1*

gene as recited in claim 103. As discussed above, the working examples only identify mutations present in the *PKHD1* gene of subjects of known ARPKD status. Although the specification further discusses the potential diagnostic utility of the identified mutations, the specification does not demonstrate that any of the identified mutations in the *PKHD1* gene can be used to reliably and reproducibly diagnose ARPKD in a subject of unknown disease status. As a result, the specification does not contain an actual reduction to practice of the claimed methods. Also, as discussed above, the claimed method is not described in the prior art, is associated with a high degree of unpredictability, and requires a high level of skill in the art for its practice. Accordingly, the ordinary artisan would not have considered the Applicant to be in possession of the claimed method.

Since Applicant's arguments were not persuasive, the rejection of claim 103 under 35 U.S.C. 112, first paragraph (written description) has been maintained.

Conclusion

5. No claims are currently allowable. It is noted that the claimed method is free of the art, but has been rejected for other reasons, specifically failure to comply with the enablement and written description requirements of 35 U.S.C. 112, first paragraph.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until

after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANGELA BERTAGNA whose telephone number is (571)272-8291. The examiner can normally be reached on M-F, 9- 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Angela M Bertagna/
Examiner, Art Unit 1637

/GARY BENZION/
Supervisory Patent Examiner, Art Unit 1637